Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 35-38, 40-41, 43-52 and 54-68 are pending in the application, with claim 35 being the sole independent claim. Claims 39 and 42 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Applicants retain the right to pursue the subject matter of the canceled claims in one or more continuing applications. Claim 35 has been amended for clarity. Support for the amendment can be found throughout the specification and the original claims. For example, support can be found in the specification at page 5, lines 21-22; page 6, lines 1-10; and page 6, lines 17-20. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Claims Free of the Prior Art

The Examiner has indicated that 42-45 and 58-63 are free of the prior art. (Paper No. 20, page 8.)

II. Objection to the Specification Under 35 U.S.C. § 132 and Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph

The Examiner has objected to Applicants' amendment of the specification under 35 U.S.C. § 132 as allegedly introducing new matter into the disclosure. (Paper No. 20, page 2.) Specifically, the Examiner has stated that:

> The added material which is not supported by the original disclosure is as follows: "random branched" at page 6, lines 1 and 4. The specification as filed gave non-limiting examples of PEI which was suitable for the invention. The specification did not explicitly exclude any form of PEI from use in the invention. For this reason, the incorporation of the sub genus "random branched" PEI constitutes new matter.

(*Id.*) Applicants respectfully traverse the rejection.

Upon reading the amendment to the specification, it is clear that the addition of the phrase "random-branched" only pertained to certain, *specified* commercially obtainable PEI and not to *all* commercially available PEI. In particular, "random-branched" was added twice to the paragraph beginning at page 6 of the specification as follows:

> Examples of commercially obtainable <u>random-branched</u> PEI with different molecular weights which is suitable within the scope of the present invention are PEI 700 D, PEI 2000 D, PEI 25000 D, PEI 750000 D (Aldrich), PEI 50000 D (Sigma) and PEI 800000 D (Fluka). BASF also market <u>random-branched</u> PEI under the brand name Lupasol® in different molecular weights (Lupasol® FG: 800 D; Lupasol® G 20 anhydrous: 1300 D; Lupasol® WF: 25000 D; Lupasol® G 20: 1300 D; Lupasol® G 35: 2000 D; Lupasol® P: 750000 D; Lupasol® PS: 750000 D; Lupasol® SK: 2000000 D).

In the first instance, rather than referring to commercially obtainable PEI generally, "random-branched" clearly only refers to certain examples of commercially obtainable PEI, *i.e.*, PEI 700D, PEI 2000 D, PEI 25000 D, etc. Similarly, as used in the second instance, "random-branched" only refers to certain, specified PEI marketed by BASF, *i.e.*, Lupasol® FG: 800

D; Lupasol® G 20 anhydrous, etc. As attested to by Dr. Manfred Ogris at paragraph 7 of the Rule 132 Declaration filed on August 28, 2001, "[a]ll the examples of PEI listed in the specification of the captioned application . . . are random branched PEI." Accordingly, it is respectfully submitted that the objection to the specification be withdrawn as *no new sub-genus has been created* by the addition of "random-branched" to the specification. As discussed above, "random-branched" was added to the specification to refer to specific commercially available species that indeed are random-branched; it was not added to limit all commercially available PEIs.

The Examiner has also rejected claims 35-52 and 54-68 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants, at the time the application was filed, had possession of the claimed invention. (Paper No. 20, page 3.) The Examiner has stated that:

> The specification as filed gave *non-limiting* examples of PEI which was suitable for the invention. However the specification did not explicitly exclude any form of PEI from use in the invention. For this reason, limitation of the claimed material to the sub-genus of "random branched" PEI constitutes new matter.

(*Id.* (emphasis in original) (citation omitted).) Applicants respectfully traverse the rejection as applied to the claims as amended.

As amended, claim 35 is limited to "random-branched" PEI having a molecular weight of about 700 D to about 2,000,000 D. Applicants assert that this subgenus (*i.e.*, the subgenus of PEI that are both "random branched" and have "a molecular weight of about 700 D to about 2,000,000 D") is not added matter as one of ordinary skill in the art would reasonably conclude, upon reading the specification, that this subgenus was in the possession

of the inventors at the time of filing *and* adequately described in the specification. Applicants' arguments supporting this assertion are provided below.

Under 35 U.S.C. § 112, first paragraph, the specification of a patent application must "contain a written description of the invention." 35 U.S.C. § 112. "The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345, 54 USPQ2d 1915, 1917 (Fed. Cir. 2000); *see also*, *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991), *reh'g, en banc, denied*, 1991 U.S. App. LEXIS 17676 (Fed. Cir. 1991)("Adequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.")(quoting *Ringo Co. v. Molins Mach. Co.*, 657 F.2d 535, 551, 211 USPQ 303, 321 (3d Cir.), *cert. denied*, 454 U.S. 1055, 102 S. Ct. 600, 70 L. Ed. 2d 591 (1981)).

Generally, the written description requirement is met if the patent specification describes the invention "in sufficient detail that one skilled in the art can clearly conclude that 'the inventor invented the claimed invention'." *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), *reh'g, en banc, denied*, 1997 U.S. App. LEXIS 31640 (Fed. Cir. 1997), *and cert. denied*, 523 U.S. 1089, 140 L. Ed. 695, 118 S. Ct. 1548 (1998)(quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)). "The test is whether the disclosure of the application relied upon reasonably conveys to a person skilled in the art that the inventor *had possession* of the claimed subject matter at the time of the earlier filing date." *Eiselstein v. Frank*, 52 F.3d

1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (emphasis added); *see also Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir.), *reh'g, en banc, denied,* 2000 U.S. App. LEXIS 12720 (Fed. Cir. 2000)("[Section § 112, [Para.] 1 ensures that, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims.").

Recently, the Federal Circuit has qualified that a demonstration of "possession" is the purpose of the written description requirement, but a mere showing of possession, or reduction to practice of the invention alone, may not always satisfy the written description requirement. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002)(*Enzo* II). The court stated:

> Application of the written description requirement . . . is not subsumed by the "possession" inquiry. A showing of "possession" is ancillary to the statutory mandate that the "specification shall contain a written description of the invention," and that requirement is not met if, despite a showing of possession, the specification does not adequately describe the claimed invention.

(*Id.* at 1330.) The court did not elaborate as to how one can adequately describe the claimed invention except by indicating that the written description requirement is satisfied by the patentee's disclosure of "'such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention.'" *Id.* at 1329. (quoting *Lockwood v. American Airlines, Inc.*,107 F.3d 1565, 1572 (Fed. Cir. 1997).

At the outset, it is true that the specification at page 5, lines 21-22, does not explicitly state that PEI of the invention having "a molecular weight of about 700 D to about 2,000,000 D" is random-branched. However, one of ordinary skill in the art would appreciate that the inventors were referring to random-branched PEI in this passage for the following reasons.

First, on the top of the very next page (*see* page 6, lines 1-10 of the specification) fourteen specific examples of commercially available PEI are described. Inventor testimony has already been made of record establishing that each of the fourteen listed examples is random-branched. (*See* paragraph 7 of Declaration of Manfred Ogris Under 37 C.F.R. §1.132, submitted August 28, 2001). *Importantly, the range of molecular weights encompassed by the specific examples of random branched PEI listed at page 6, lines 1-10, of the specification is 700 to 2,000,000 D.* Thus, it would have been clear to the skilled artisan that the text at page 5, lines 21-22, and the text at page 6, lines 1-10, were intended to be read together. That is, the 700 to 2,000,000 D range of PEI referred to at page 5, lines 21-22, was clearly extracted from the fourteen examples of *random-branched* PEI listed in the very next passage in the specification. Accordingly, a fair reading of the specification is that the inventors were in possession of and had described random-branched PEI with a molecular weight of 700 to 2,000,000 D. This reading of the specification is supported by the accompany declaration of Dr. Christian Plank, an expert in the field of gene delivery systems. In particular, at paragraph 9, Dr. Plank states:

> As discussed, the molecular weight range indicated in the specification at page 5, lines 21-22, was clearly contemplated in connection with the examples of commercially obtainable PEI listed on the following page. Each of the examples of commercially obtainable PEI has a molecular weight of about 700 D to about 2,000,000 D and is random-branched.

In his opinion, "when the specification is read in its entirety, one of ordinary skill in the art would reasonably conclude that the inventors were in possession of and have described random-branched PEI having a molecular weight of about 700 D to about 2,000,000 D." ¶ 9, Declaration of Christian Plank Under 37 C.F.R. § 1.132.

Secondly, Applicants have made statements about the properties of the PEI/DNA/polymer complexes that relate to observations made using random-branched PEI. Following the description of the molecular weight range of the PEI of the claimed complexes, the specification indicates that:

> Larger PEI molecules yield optimum transfection efficiency after complexing with DNA even at lower N/P ratios, and result in very good transfection efficiency in general. Smaller molecules, of which a larger amount is needed for complexing, for the specified amount of DNA, have the advantage of lower toxicity, albeit with lower efficiency.

(Specification, page 5, lines 22-29.)

Examples 1-15 of the specification use two different molecular weights of random-branched PEI. The methods for forming complexes taught in examples 1-14 use 800,000 D PEI from Fluka and the method taught in Example 15 uses 25,000 D PEI from Aldrich. Both of these PEIs are found in the list disclosed at page 6, lines 1-10, of the specification and both have a random-branched structure. When the teachings of the specification are viewed in its entirety, it is clear that the above-quoted excerpt regarding transfection efficiency relates to the random-branched form of PEI because all of the specific examples of PEI provided in the specification are random-branched.

Thirdly, Applicants emphasize that one of ordinary in the art would understand that the term "PEI" or "polyethyleneimine," when used alone and without any modifying adjective or other descriptive term, to mean random-branched PEI, which is the "regular" PEI that has been commercially available for decades. *See, e.g.*, Melamed, S. *et al.*, *J. Pharm. Sci.* *66:*899-901 (1977). To support this assertion, Applicants have provided a Declaration by one of the inventors attesting to this fact.

Despite these assertions, the Examiner has stated that the "position of the PTO is that 'PEI' is a generic term encompassing all types of polyethyleneimine polymers including linear, random short branched, random long branched, regular comb branched, regular star branched, dendritic, and hyper comb branched." (Paper No. 18, page 14.) However, the Examiner has proffered no evidence to support this broad assertion. Rather, the Examiner has attempted to use Applicants' own exhibits as evidence to support the Examiner's position. Applicants submit that the Examiner misreads these references.

As discussed in Dr. Ogris' Declaration, Coll *et al.*, *Hum. Gen. Therapy* 10:1659-66 (1999) refer to the linear PEI used in the experiments as L-PEI or "linear polyethyleneimine." Although Coll *et al.* refer to L-PEI as simply "polyethyleneinime" in one instance (page 1660, third full paragraph), this fact alone does not vitiate Applicants' assertions because—when the document *is read as a whole*—it is manifestly clear that the authors are careful to specifically articulate what type of PEI is being used, *i.e.*, the linear form of the polymer. The title of the publication recites "linear polyethylenimine" and "L-PEI" or "linear polyethylenimine" is recited eight times in the abstract. Indeed, Coll *et al.* refer to the PEI of his experiments as "L-PEI" or "linear polyethylenimine" at least 15 times on the first page alone and many more references to L-PEI or linear polyethylenimine are made in the following pages. When Coll *et al.* is read as an entire document, it is clear that the reference is careful to specifically articulate what type of PEI is being used. Applicants have provided the Examiner with the *entire* Coll *et al.* document to support Applicants' assertions and not simply a *sentence or two* within the document. To that end, nothing in Coll *et al.* contradicts the assertion that one of ordinary in the art would understand the term "PEI" or

"polyethyleneimine," when used alone and without any modifying adjective or other descriptive term, to mean random-branched PEI.

The Examiner has asserted that Godbey *et al.* contradict Applicants' assertion as to the art-recognized meaning of PEI. (Paper No. 18, page 14.) Applicants respectfully disagree. There is nothing in Godbey *et al.* that contradicts Applicants' assertions. As the Examiner correctly indicates, Godbey *et al.* teach that PEI comes in two forms: linear and branched. (Godbey *et al.*, page 150, column 1.) But Godbey *et al.* also teach that:

> The branched form of PEI has yielded significantly greater success in terms of cell transfection, and is therefore the standard form of PEI that has been used for gene delivery. Unless otherwise noted, all references to PEI ascribe to the branched form of the molecule.

(*Id.* at column 2.)

Figure 1 of Godbey *et al.* shows a structure of "Branched PEI." The structure is the random-branched form of PEI. In view of these teachings in Godbey *et al.*, Applicants assert that Godbey *et al.*, rather than contradicting Applicants' assertions, actually support Applicants' assertions about the meaning of the term "PEI" in the art of gene delivery. That is, one of ordinary skill in the art would recognize the term to refer to the random-branched form of the polymer absent any modifying adjective or other descriptive term or phrase.

With respect to Klotz *et al.*, the Examiner is again correct in noting that Klotz *et al.* teach that PEI is a "highly branched water soluble polymer." (Klotz *et al.*, page 4753, column 1.) But Klotz *et al.* also provide a schematic representation of the "highly branched" PEI. The schematic representation shows the PEI as a random-branched polymer. Thus, the definition of PEI provided by Klotz *et al.* is not as broad as the Examiner suggests and would exclude the highly ordered, non-random forms of PEI disclosed by Yin *et al.* and Tomalia

et al. Further, nothing in Klotz *et al.* contradicts Applicants' assertions of the art-recognized meaning of the term "PEI." After describing the general structure of the PEI, they note that the specific PEI used in their experiments was PEI-600. Applicants fail to see how these teachings contradict Applicants' assertion of the art-recognized meaning of the term "PEI."

III. Conclusion

Based on the above, it is clear that Applicants had possession of and adequately described random-branched PEI having a molecular weight of about 700 D to about 2,000,000 D at the time of filing. Not only does the specification specifically teach that the PEI of the claimed invention has a molecular weight of about 700 D to about 2,000,000 D, the specification provides commercially obtainable examples of PEI that fall within the indicated molecular weight range. As attested by two individuals familiar with the art, each and every example provided in the specification has a random-branched macromolecular structure. From these teachings in the specification, it is clear that one of ordinary skill in the art would reasonably conclude that Applicants' were in possession of random-branched PEI having a molecular weight of about 700 D to about 2,000,000 and that the specification adequately supports PEI having these limitations. This is particularly evident in view of the fact that one of ordinary skill in the art would understand the term "PEI" or "polyethyleneimine," when used alone and without any modifying adjective or other descriptive term, to mean random-branched PEI, which is the "regular" PEI that has been commercially available for decades.

In view of the above, Applicants respectfully request that the Examiner enter the amendment to the specification. Additionally, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 35-41, 46-52, 54, 55, and 64-68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Curiel *et al.*, U.S. Patent No. 6,077,663 in view of Boussif *et al.*, *Proc. Nat. Acad. Sci.*, 92:7297-7301 (1995). Applicants respectfully traverse the rejection.

Solely to advance prosecution and not in acquiescence to the Examiner's rejection, Applicants have amended claim 35 to incorporate the limitations of claim 42. Claim 35 presently requires that the hydrophilic polymer be selected from the group consisting of polyethylene glycols (PEG), polyvinylpyrollidones, polyacrylamides, polyvinylalcohols, and copolymers thereof. Neither Curiel *et al.* nor Boussif *et al.* teach or suggest the use of these polymers covalently attached to PEI. Indeed, the Examiner has indicated that claim 42 is free of the prior art. (Paper No. 20, page 8.) Thus, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claims 56 and 57 as allegedly unpatentable over Curiel *et al.* and Bousiff *et al.* in further view of Ezzidine *et al.*, *New Biol* 3(6): 608-614 (1991). Applicants respectfully traverse the rejection.

The deficiencies of Curiel *et al.* and Boussif *et al.* have been discussed above. Ezzidine *et al.* do not cure these deficiencies. Accordingly, the combination of references

does not render the claims unpatentable. Applicants, therefore, respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Eric K. Steffe
Attorney for Applicants
Registration No.36,688

Date: 3/19/03

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Version with markings to show changes made

The application is sought to be amended as follows:

In the Claims:

35. (Twice amended) Complexes of nucleic acid and random-branched polyethyleneimine (PEI), characterized in that the PEI is modified with a hydrophilic polymer covalently coupled thereto,

wherein said PEI has a molecular weight of about 700 D to about 2,000,000 D,

and wherein said hydrophilic polymer is selected from the group consisting of polyethylene glycols (PEG), polyvinylpyrollidones, polyacrylamides, polyvinylalcohols, and copolymers thereof.

[wherein said complexes are formed by (a) mixing solutions of nucleic acid and PEI and afterwards, covalently modifying the PEI with hydrophilic polymer or (b) mixing solutions of nucleic acid and PEI, which has been covalently modified with hydrophilic polymer before said mixing.]

39. (Canceled)

42. (Canceled)

43. (Amended) Complexes according to claim [42] 35, characterised in that the hydrophilic polymer is PEG.

44. (Amended) Complexes according to claim [42] 35, characterised in that the molecular weight of the hydrophilic polymer is about 500 D to about 20,000 D.

#27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 2149
WAGNER *et al.*	Art Unit: 1635
Appl. No. 09/446,317	Examiner: Schnizer, R.
§ 371 Date: April 17, 2000 (CPA Filed: December 29, 2000)	Atty. Docket: 0652.2010000/EKS/PSC
For: **Complexes for Transporting Nucleic Acid Into Eukaryotic Higher-Cells**	

Declaration of Christian Plank Under 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Christian Plank, Ph.D., a citizen of Austria, do hereby declare and say:

1. I received my education at the University of Vienna, Austria, where I earned my Ph.D in Biochemistry. My training continued at the University of California, San Francisco, where I was a postdoctoral fellow. My postdoctoral research involved development of peptide-based gene delivery systems and the characterization of biophysical properties of gene vectors and their interaction with blood components. A copy of my curriculum vitae is attached as Exhibit 1.

2. I am currently employed at the Technical University of Munich, Germany, Institute of Experimental Oncology, where I hold the position of a Group Leader. My work involves the development of synthetic nanoconstructs for gene delivery.

3. I have been retained by Boehringer Ingelheim GmbH, assignee of the captioned application, to serve as an expert in the field of gene delivery systems and to provide comments regarding the teachings of the specification of the captioned application. I understand the captioned

application to be a U.S. national phase application of international application PCT/EP98/03679, which was filed on June 18, 1998. I also understand that the captioned application claims priority to German application DE 197 26 186.8, which was filed on June 20, 1997.

4. I have carefully read the specification and the claims of the captioned application. I understand the principle claim of the captioned application to be drawn to complexes of nucleic acid and polyethyleneimine (PEI), wherein said PEI is covalently modified with a hydrophilic polymer. The specification refers to these complexes as "DNA/PEI/polymer complexes" and teaches that these complexes are useful as gene transfer systems. (Page 4, lines 31-33; page 4, lines 23-26.) In my opinion, one of ordinary skill in the art would reasonably conclude, after reading the specification, that the inventor was in possession of and had described DNA/PEI/polymer complexes, wherein the PEI has a random-branched macromolecular structure and a molecular weight of about about 700 D to about 2,000,000 D.

5. I come to this conclusion because the specification specifically states that the PEI contained in the DNA/PEI/polymer complexes has a molecular weight of about 700 D to about 2,000,000 D. (Page 5, lines 21-22.) As examples of commercially obtainable PEI suitable within the scope of the invention, the specification lists PEI 700 D, PEI 2000 D, PEI 25000 D and PEI 750000 D from Aldrich; PEI 50000 D from Sigma; PEI 800000 D from Fluka; and BASF products Lupasol ® FG: 800 D, Lupasol ® G 20 anhydrous: 1300 D, Lupasol ® WF: 25000 D, Lupasol ® G 20: 1300 D, Lupasol ® G 35: 2000 D, Lupasol ® P: 750000 D, Lupasol ® PS 750000 D and Lupasol ® SK: 2000000 D. (Page 6, lines 1-10.) The molecular weight range of the commercially obtainable PEI examples listed at page 6 correspond to the molecular weight range indicated on the previous page. It is clear to me that the inventors extracted the molecular weight range indicated on page 5 of the specification from the commercially obtainable examples listed on the following page, each of which has a random-branched structure.

6. I also note that in Examples 1-14 of the specification, 800,000 D PEI from Fluka was used to form DNA/PEI/polymer complexes. The method of producing the DNA complexes outlined in Example 1 is repeated to produce the various complexes formed in Examples 2-14. In Example 15 of the specification, PEI having a molecular weight of 25,000 D from Aldrich was used to form EGF-modified PEI/DNA complexes. Both the 800,000 D PEI and the 25,000 D PEI used in the Examples are found in the list of commercially obtainable PEI taught in the specification at page 6, lines 1-10. As discussed above in ¶ 5, both of the PEI used in the Examples have a random-branched macromolecular structure.

7. I further note that the specification teaches that the DNA/PEI/polymer complexes of the invention may be prepared by various methods. In a preferable method, DNA and PEI are first complexed by mixing dilute solutions containing each and then, e.g., after a maturation period of about 20-40 minutes, performing a reaction with the hydrophilic polymer. (Page 8, lines 25-32.) In another method, complexes are obtained from dilute solutions using PEI which has already been covalently coupled to a polymer. (Page 10, lines 6-11.)

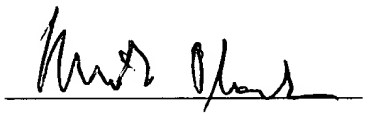
8. It is my opinion that the methods taught in the specification and Examples 1-15 are representative of methods which could be used to form DNA/PEI/polymer complexes using the commercially obtainable PEI taught in the specification, i.e., PEI having a random-branched structure and a molecular weight between about 700 D to about 2,000,000 D. Also, it is my opinion that it would not require undue experimentation to make and use DNA/PEI/polymer complexes, wherein the PEI is selected from the list found at page 6, lines 1-10, of the specification, given the teachings of the specification and the representative examples provided in the specification.

9. As discussed, the molecular weight range indicated in the specification at page 5, lines 21-22, was clearly contemplated in connection with the examples of commercially obtainable PEI listed

on the following page. Each of the examples of commercially obtainable PEI has a molecular weight of about 700 D to about 2,000,000 D and is random-branched. In addition, all of the example methods use random-branched PEI having a molecular weight within this range. In my opinion, these methods are representative of methods which could be used to generate PEI/DNA/polymer complexes, wherein the PEI has a random-branched structure and molecular weight of about 700 D to about 2,000,000 D. Based on the above, I believe that when the specification is read in its entirety, one of ordinary skill in the art would reasonably conclude that the inventors were in possession of and have described random-branched PEI having a molecular weight of about 700 D to about 2,000,000 D.

10. My conclusion is further supported by the fact that the term "PEI" or "polyethyleneinime" was, as of the filing date of the application, understood in the art to refer to the random-branched form of the PEI polymer, which is the regular PEI that was commercially available at the time of filing of the application.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patents issued thereupon.



Dr. Christian Plank

02/27/2003

Date